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NCCN Guidelines Panel: Breast Cancer

On behalf of Puma Biotechnology, Inc., I respectfully request the NCCN Breast Cancer Guideline Panel review the enclosed recent presentation for NERLYNX® (neratinib).

Specific Changes: please consider including neratinib in the treatment algorithm (as opposed to the footnote) as extended adjuvant treatment for patients with HR-positive, HER-2 positive disease who are within 1 year of completing trastuzumab-based adjuvant therapy in the following sections:

- Systemic Adjuvant Treatment: Hormone Receptor-Positive - HER2-Positive Disease (BINV-5)
- Preoperative Systemic Therapy: Adjuvant Therapy (BINV-14)
- Preoperative Systemic Therapy for Inoperable or Locally Advanced Breast Cancer (Non-Inflammatory) (BINV-16)

FDA Clearance: neratinib has been approved for extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy.[1]

Rationale: Gnant et al. presented exploratory analyses from the randomized, multicenter, international Phase 3 extended adjuvant study of neratinib examining safety and efficacy in subjects with HR-positive, HER2-postive disease who initiated treatment within 1 year of completing trastuzumab-based adjuvant treatment.[2] The European Union recently granted marketing authorization for neratinib in this patient population.[3]

- Of the 2840 subjects in the ITT population (neratinib, n=1420; placebo, n=1420), 1334 had HR-positive disease and were randomized to start study treatment within 1 year of completing trastuzumab (neratinib, n=670; placebo, n=664)
- In the subjects with HR-positive disease who started neratinib within 1 year of completing trastuzumab:
  - There was an absolute iDFS benefit of 4.5% with neratinib after 2 years of follow-up (HR 0.49; 95% CI 0.30−0.78; p=0.002); iDFS was 95.3% in neratinib-treated subjects and 90.8% in placebo-treated subjects
  - This finding was durable at 5 years, with an absolute iDFS benefit of 5.1% (HR 0.58; 95% CI 0.41−0.82; p=0.002); iDFS was 90.8% in neratinib-treated subjects and 85.7% in placebo-treated subjects
  - All prespecified secondary endpoints were also significantly improved
  - The profile and frequency of treatment-emergent adverse events in this population were similar compared with the ITT population; the most common grade 3 treatment-emergent adverse events in this population were diarrhea (neratinib, 39% vs placebo, 1%), nausea (1% vs <1%), and fatigue (2% vs <1%)

We would like to acknowledge the contributions of NCCN panel members who are also co-authors on this presentation.

Sincerely,

Deepa Lalla

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References

1. NERLYNX® (neratinib) tablets [Prescribing Information, June 2018] Puma Biotechnology, Inc., Los Angeles, CA. https://nerlynx.com/pdf/full-prescribing-information.pdf

2. Gnant M, Martin M, Holmes FA, et al. Efficacy of neratinib in hormone receptor-positive patients who initiated treatment within 1 year of completing trastuzumab-based adjuvant therapy in HER2+ early stage breast cancer: subgroup analyses from the phase III ExteNET trial. Presented at the 41st Annual San Antonio Breast Cancer Symposium (SABCS), San Antonio, TX. Poster #P2-13-01. December 4–8, 2018

3. NERLYNX® (neratinib) tablets [European Public Assessment Report (EPAR) September 2018] Puma Biotechnology, Ltd., Bristol, UK. https://www.ema.europa.eu/medicines/human/EPAR/nerlynx